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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,764	10/03/2005	Young Min Kim	Q90374	4254
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SUGHRUE MION, PLLC 2100 PENNSYLVANIA AVENUE, N.W. SUITE 800 WASHINGTON, DC 20037			EXAMINER NIEBAUER, RONALD T	
			ART UNIT	PAPER NUMBER
			1654	
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			10/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/551,764

Applicant(s)

KIM ET AL.

Examiner

Ronald T. Niebauer

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 August 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants amendments and arguments filed 8/22/07 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claim 12 remains withdrawn. Claims 1-11 remain under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

(Maintained in part/Necessitated by amendment) Since the claims have been amended, a new rejection adapted to the claims is recited here.

Claims 1-11 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As amended claim 1 recites 'wherein the first PEG is covalently bonded to the polypeptides at an N-terminal residue or a C-terminal residue of the polypeptides'. From claim 1 it remains unclear as to whether the PEG can be attached to any residue (note the recitation of an N-terminal residue, not the N-terminal residue) in the N-terminal or C-terminal domain or if it is to be attached to the N-terminal residue or the C-terminal residue (compare previous office action page 4 4th paragraph).

Claim 2 recites 'bonded to the respective N-terminal of the polypeptide'. It is unclear as to whether the PEG can be attached to any residue in the N-terminus (note that N-terminal is

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recited in the claim not N-terminal residue) or if the PEG is to be attached to the N-terminal residue. The term 'N-terminal' or 'N-terminus' (a broad term) is often used to refer to a domain of a protein while the phrase 'the N-terminal residue' (a specific term) is used to refer to a single particular residue (compare previous office action page 4 4th paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

(Maintained in part/Necessitated by amendment) Since the claims have been amended, a new rejection adapted to the claims is recited here using the same references as in the previous rejection.

Claims 1-11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Braxton (US 5,766,897, cited previously) and Kay et al. (US 2002/0077294, cited previously).

Braxton teaches a PEG-polypeptide dimeric complex (column 13 line 56) of the general formula R1-S-PEG-S-R2 where R1 and R2 may represent the same or different proteins. Braxton teaches that human growth hormone (hGH) (Table IA and column 12 line 1) is a polypeptide that can be a part of the complex (compare claim 4 limitation) which would result in hGH-firstPEG-hGH. Braxton further teaches that PEG can be attached at particular residues (column 12 line 49). Braxton teach that the residue could be naturally present in the protein or could be

introduced by site-directed mutagenesis (column 13 line 64-66). Braxton teaches that the PEG linker/moiety (i.e. first PEG) may be in the range of 0.2-20 kDa (column 12 line 50) (compare claim 6-7 limitation). Braxton teaches that a lysine residue is typically reacted with PEG (column 2 line 12) (compare claim limitation 3).

Braxton does not expressly teach further pegylation of the PEG dimer with PEG of a different molecular weight. Braxton does not expressly teach the PEG groups such as those recited in claim 5 and 8 of the current invention.

Kay et al. teach polypeptide derivatives in which a protein is linked to a nonproteinaceous moiety (e.g. a polymer) in order to modify properties (section 0146). Kay et al. teach PEG as an example of the polymer (section 0148). Kay et al. teach PEG modification at the amino terminus of the protein (section 0157) (compare claim limitation 2). Specifically, Kay et al. teach protein dimers via PEG crosslinkers (section 0161). Kay et al. teach the polymer (i.e. PEG) having a molecular weight of 2-100kDa (section 0149) (compare claim 10-11 limitation). Kay et al. teach propionaldehyde (i.e. propionic aldehyde) groups on PEG (section 0148) (compare claim limitation 5). Kay et al. teach reactive groups such as maleimide (section 0154) (compare claim limitation 8). Kay et al. teach that the polymers may be branched or unbranched (section 0149) (compare claim limitation 9).

One would be motivated by Braxton to obtain a polypeptide-first PEG-polypeptide dimeric protein (i.e. hGH-firstPEG-hGH) since Braxton teaches such a protein. Braxton teach that pegylation of a protein improves for example, half-life (column 25). Kay also teach that pegylation of a protein is desirable (section 0156) and teach PEG (i.e. second PEG) having a molecular weight of 2-100kDa (section 0149). Hence, the pegylation of the dimer (hGH-PEG-

hGH) would be desirable and result in secondPEG-hGH-firstPEG-hGH-secondPEG where the molecular weight of first PEG is 0.2-20 kDa as cited above and the molecular weight of the second PEG is 2-100kDa as cited above. Therefore the ranges of the PEG molecular weights are such that the second PEG molecule can have a larger molecular weight than the first.

Further, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. PEG molecular weights), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP § 2145.05).

Regarding the site of the first PEG linkage, since Braxton and Kay both teach dimers one would be motivated to substitute the method of Kay (section 0161) to obtain PEG dimers via amino-terminal crosslinks at the amino terminus. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

It has been recently held that "Neither §103's enactment nor *Graham's* analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art." *KSR v. Teleflex*, 550 U.S. ___, 82 USPQ2d 1385, 1389 (2007). The KSR court stated that "a combination of familiar elements according to

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known methods is likely to be obvious when it does no more than yield predictable results.” KSR at 1389. The Supreme Court stated that there are “[t]here cases decided after Graham [that] illustrate this doctrine.” KSR at 1395. “In United States v. Adams, 383 U.S. 39, 40, 148 USPQ 479 (1966) . . . [t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.” KSR at 1395. Thus, the mere substitution of one known element for another to obtain a predictable result is obvious.

Furthermore, The KSR court concluded that “obvious to try” may be an appropriate test under 103. The Supreme Court stated in KSR

When there is motivation

“to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.” KSR Int’l Co. v. Teleflex Inc., 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

In the instant case, the prior art teach the claimed elements. One of skill in the art could have combined the elements as claimed by known methods and the combination would have yielded predictable results to one of ordinary skill at the time of the reference. In particular, one would have combined the hGH-firstPEG-hGH dimer of Braxton with the teachings of Kay to arrive at a pegylated dimer. Further, the substitution of Kays method of amino-terminal PEG crosslinks to obtain dimers for Braxtons method of obtaining dimers would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

For purposes of examination the location of the first PEG linkage (see 112 2nd above) has been interpreted broadly to include any N-terminal region residue (for claim 1). As noted above, Kay teach (section 0161) PEG dimers via amino-terminal crosslinks at the amino terminus.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Response to Arguments 103 rejection

Since the claims have been amended, a new rejection adapted to the claims is recited above using the same references as in the previous rejection. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that the references do not teach the claimed elements. Applicants argue that the prior art does not teach a homodimer used to minimize the decrease of the biological activity. Applicants argue that the references do not teach, for example the use of a first PEG and a second PEG.

Applicant's arguments filed 8/22/07 have been fully considered but they are not persuasive.

Since the claims are drawn to a product, the intended use (to minimize decrease in biological activity) (see MPEP section 2111.02 II) does not result in a structural difference and does not limit the claim. Further, applicant is arguing about the biological activity which is an unclaimed feature.

Since the rejection is a multiple reference 103 rejection the elements of the claims are taught or obvious from a combination of the references. Therefore, the use of a first and second PEG is obvious as discussed above.

For these reasons, the reasons above, and the reasons set forth previously the rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ronald T. Niebauer whose telephone number is 571-270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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